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09/134,014	08/14/1998	WILHELM GRUISSEM	018941-00020	7338

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EXAMINER	
FOX, DAVID T	
ART UNIT	**PAPER NUMBER**
1638	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/134,014	Gruissem et al
Examiner	Group Art Unit
Fox	1638

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -3- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 11/10/99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-31 is/are pending in the application.

Of the above claim(s) 13-31 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-12 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1638. The application has been transferred to Examiner David Fox. The delay in prosecution is regretted.

Applicant's election of Group I in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The specification is objected to for its reference to color figures on page 10, lines 24-32, while only black-and-white photographs have been submitted. In addition, the boundary of the luciferase gene is unclear in the figures.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in its recitation of "polynucleotide sequence comprising a polypeptide sequence" which is confusing. Replacement of "comprising" after "sequence" in line 4 with --encoding-- would obviate this rejection. Dependent claims are included in the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for identifying homologous recombination in plant cells comprising transformation with a fusion protein-encoding product comprising any non-selectable reporter gene-encoding sequence ligated to any other protein sequence, wherein various types of homologous recombination events are obtained, and wherein a multitude of endogenous genes are inactivated. In contrast, the specification only provides guidance for a method for identifying homologous recombination via the use of a selective reporter gene such as the NPTII gene conferring kanamycin resistance (see, e.g, Figures 1B, 1C and 2; page 18 of the specification), wherein at least "non-reciprocal" (synonymous with "gene conversion") recombination and recombination between the fusion gene and the endogenous gene were not observed (see, e.g., page 22 of the specification, top paragraph). No guidance was provided for the inactivation of any endogenous gene or for the obtention of the various types of homologous recombination events of claims 8-10 and 12.

Homologous recombination in transformed plant cells and plants is unpredictable. Risseeuw et al teach that transgenes inserted via homologous recombination may be unstable in

cultured plant cells (see, e.g., page 717, Abstract). Thykjaer et al teach that the use of non-selectable or even selectable markers as part of the constructs also comprising endogenous genes results in the lack of identification or maintenance of homologous recombination events (see, e.g., page 523, Abstract).

Given the claim breadth, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate methods for identifying and obtaining homologous recombination in plant cells transformed with a genetic construct that does not contain a selectable marker gene. Furthermore, undue experimentation would have been required to develop and evaluate methods for obtaining and identifying a variety of different types of homologous recombination events or the inactivation of a multitude of endogenous genes.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3, 4, and 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Staub et al.

The claims are drawn to a method comprising plant cell transformation with a construct comprising a fusion polynucleotide encoding a non-selective reporter protein ligated to a polypeptide of interest for the obtention and identification of homologous recombination, wherein the construct does not comprise sequences required for the expression of the fusion polynucleotide, and wherein the homologous recombination event is identified by screening plants regenerated from the transformed plant cell for the presence of the fusion polynucleotide gene product. Claim 11 is drawn to inactivation of an endogenous gene.

Staub et al teach a method for plant cell transformation with a construct comprising a promoterless fusion polynucleotide comprising a portion of the rbcL protein and the non-selectable beta-glucuronidase marker protein, wherein seedlings and plants were regenerated from the transformed cells, and wherein the regenerated plants and plant tissues were screened for the production of the rbcL/GUS fusion protein produced by homologous recombination with the plastid genomic region containing the rbcL structural gene and endogenous promoter (see, e.g., page 845, column 2, bottom paragraph; page 846, column 1 and first and second full paragraphs of column 2; page 847, column 1 and first full paragraph of column 2; page 848, column 1, top paragraph). The production of an rbcL/GUS fusion protein would inactivate the rbcL gene because a discrete rbcL protein able to combine with the rbcS subunit, for the production of active ribulose bisphosphate carboxylase enzyme, would not be formed.

Claims 1-3, 7-10 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Odell et al (U.S. 5,658,772 filed July 1994).

The claims are drawn to an *Agrobacterium*-derived T-DNA vector-mediated method for plant cell transformation with a construct comprising a fusion polynucleotide encoding a reporter protein ligated to a polypeptide of interest for the obtention and identification of homologous recombination, wherein the construct does not comprise sequences required for the expression of the fusion polynucleotide, and wherein the homologous recombination event is identified by screening plants regenerated from the transformed plant cell for the presence of the fusion polynucleotide gene product, and wherein the plant cell is *Arabidopsis*.

Odell et al teach an *Agrobacterium*-mediated method for plant cell transformation with a construct comprising a *loxP* site ligated to a gene encoding a selectable neomycin phosphotransferase II reporter protein conferring kanamycin resistance, wherein said selectable protein is fused with a portion of the LEU2 protein by virtue of the *loxP* site containing a portion of the *leu2* protein-encoding region, wherein *Arabidopsis* was one of the plant species transformed, wherein the initial construct lacked sequences necessary for expression of the fusion polynucleotide (i.e. sequences comprising promoter sequences directly ligated to a transcription start site) by virtue of the presence of a polyadenylation site between the fusion polynucleotide transcription start site and the promoter, and wherein homologous recombination between the *loxP* sites flanking the polyadenylation region was detected by the presence of the fusion protein comprising the kanamycin resistance protein in transformed plant cells and plant tissues (see, e.g., Figures 1C and 2B; column 8; columns 21-22; columns 24-27; column 34, line 55 through column 36, line 7).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swoboda et al taken with Lyznik et al.

The claims are drawn to an *Agrobacterium*-mediated method of plant cell transformation with a fusion polynucleotide sequence encoding a protein of interest ligated to a non-selectable marker protein, wherein said fusion polynucleotide sequence lacks sequences necessary for expression thereof, for the identification of homologous recombination in transformed cells and plants regenerated therefrom. Methods of transforming *Arabidopsis* cells are also claimed.

Swoboda et al teach a method for identifying homologous recombination comprising the *Agrobacterium*-mediated transformation of *Arabidopsis* cells with a fusion polynucleotide

comprising a portion of the GUS gene ligated to a portion of the CaMV ORF V encoding the first 29 amino acids thereof, wherein whole regenerated plants were assayed for the presence of the GUS-containing fusion protein, and wherein the non-selectable marker had the advantage of allowing recombination assays in whole plants (see, e.g., page 484, column 2, bottom three paragraphs; page 485; page 486, Figure 2; page 487, column 2, bottom paragraph; page 488, column 2, penultimate paragraph).

Swoboda et al do not teach a promoterless construct.

Lyznik et al teach a method for the identification of homologous recombination comprising plant cell transformation with a promoterless fusion polynucleotide construct comprising a GUS gene fused to an intron, wherein recombination was detected by detection of the GUS protein, and wherein the use of a promoterless fusion polynucleotide construct facilitated the detection of recombination by virtue of a strong endogenous promoter (see, e.g., page 209, column 1; page 210, column 2; page 211; page 212, column 1, second full paragraph; page 214, Figures 6-7; page 215, Figures 8-9; page 216, column 1, bottom paragraph).

It would have been obvious to one of ordinary skill in the art to use the fusion polynucleotide-mediated method of detecting homologous recombination in plant cells taught by Swoboda et al, and to modify that method by incorporating the promoterless construct taught by Lyznik et al, as suggested by each reference.

Claims 1-10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swoboda et al taken with Lyznik et al, further in view of Ow et al.

The claims are drawn to an *Agrobacterium*-mediated method of plant cell transformation with a fusion polynucleotide sequence encoding a protein of interest ligated to a non-selectable marker protein including luciferase, wherein said fusion polynucleotide sequence lacks sequences necessary for expression thereof; for the identification of homologous recombination in transformed cells and plants regenerated therefrom.

Swoboda et al taken with Lyznik et al teach a method for identifying homologous recombination in plants comprising transformation with a promoterless fusion polynucleotide encoding a protein of interest ligated to a non-selectable reporter gene as discussed above, but do not teach the use of the gene encoding the non-selectable protein luciferase.

Ow et al teach plant cell transformation with the luciferase gene and its use to detect transformation events in plant cells and whole plants, and also suggest the use of the gene in fusion constructs and the use of video imaging for detection of the protein, wherein the luciferase reporter protein has the advantages of speed and ease of detection (see, e.g., page 856; paragraph bridging pages 857 and 858; page 858, Figure 5; page 859, column 1, bottom paragraph).

It would have been obvious to one of ordinary skill in the art to utilize the method for identifying homologous recombination in plants comprising transformation with a promoterless fusion polynucleotide encoding a protein of interest ligated to a non-selectable reporter gene as taught by Swoboda et al taken with Lyznik et al, and to modify that method by incorporating the non-selectable luciferase gene taught by Ow et al, as suggested by Ow et al.

Claims 1-4 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swoboda et al taken with Lyznik et al, further in view of Miao et al.

The claims are drawn to an *Agrobacterium*-mediated method of plant cell transformation with a fusion polynucleotide sequence encoding a protein of interest ligated to a non-selectable marker protein, wherein said fusion polynucleotide sequence lacks sequences necessary for expression thereof, and wherein homologous recombination results in the inactivation of an endogenous gene, for the identification of homologous recombination in transformed cells and plants regenerated therefrom.

Swoboda et al taken with Lyznik et al teach a method for identifying homologous recombination in plants comprising transformation with a promoterless fusion polynucleotide encoding a protein of interest ligated to a non-selectable reporter gene as discussed above, but do not teach the inactivation of an endogenous gene.

Miao et al teach the use of the GUS gene to identify homologous recombination in *Arabidopsis* plants transformed with an *Agrobacterium* -derived plasmid vector comprising the GUS gene and also comprising a fusion polynucleotide comprising the kanamycin resistance gene ligated to a portion of the endogenous TGA3 gene, wherein homologous recombination (and concomitant TGA3 gene inactivation) were detected by kanamycin resistance and lack of GUS protein expression, and wherein the technique has the advantages of targeted mutation of non-selectable endogenous genes (see, e.g., page 359, paragraph bridging the columns; paragraph

bridging pages 359 and 360; page 360, Figure 1 and column 2; page 361, Figure 2 and column 1; page 363, paragraph bridging the columns; page 364, column 1, top two paragraphs).

It would have been obvious to one of ordinary skill in the art to utilize the method for identifying homologous recombination in plants comprising transformation with a promoterless fusion polynucleotide encoding a protein of interest ligated to a non-selectable reporter gene as taught by Swoboda et al taken with Lyznik et al, and to modify that method by incorporating the inactivation of an endogenous gene as taught by Miao et al, as suggested by Miao et al.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David T. Fox whose telephone number is (703) 308-0280. The examiner can normally be reached on Monday through Friday from 10:30AM to 7:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (703) 306-3218. The fax phone number for this Group is (703) 872-9306. The after final fax phone number is (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 15, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638